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(54) Aspartyl dipeptide amide derivatives and sweeteners

(57) The present invention provides a low-calory sweetener having a high stability, an excellent safety and an excellent sweetness.

The object of the present invention is accomplished by the preparation of novel aspartyldipeptidoamide derivatives such as α-L-aspartyl-D-isoleucine (R)-α-methylthiomethylbenzylamide and the like or salts thereof, as well as a sweetener containing the same as an active ingredient.

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Description

Field of the Invention

The present invention relates to novel aspartyl dipeptide amide derivatives and salts thereof as well as a sweetener containing the same as an active ingredient.

Background of the Invention

In recent years, eating habits have been improved to a high level, and fatness caused by excessive intake of sugar and diseases accompanied by the fatness have been at issue. Therefore, the development of a low-calory sweetener that replaces sugar has been in demand. As a sweetener that has been widely used at present, there is aspartame which is excellent in terms of a safety and sweetness properities. However, it involves a problem of a stability. In order to improve the stability and the sweetness intensity, aspartyl-D-amino acid amide derivatives free from an ester linkage were studied. For example, the compounds described in U.S. Patent No. 4,411,925 or 5,286,509 were thus discovered. Meanwhile, it is described in French Patent No. 2,697,844 that aspartyldipeptide derivatives in which an alkyl group has been introduced into an amino group exhibits an extremely increased degree of sweetness. However, these compounds do not satisfy the stability.

Problems To Be Solved by the Invention

The present invention is to provide novel aspartyl dipeptide amide derivatives and salts thereof which are obtained by using easily-obtainable amino acid and amine components and which exhibit a high stability and an excellent safety, as well as a low-calory sweetener containing the same as an active ingredient.

Means for Solving the Problems

In order to solve the above-mentioned problems, the present inventors have assiduously conducted investigations with respect to amine components of various aspartyl dipeptide amides having a satisfactory stability, and have consequently found compounds which exhibit a higher degree of sweetness than conventional aspartyl dipeptide amides. This finding has led to the completion of the present invention.

$$R_1\text{-}NHC^1H(CH_2COOH)CO\text{-}X\text{-}NH\text{-}C^2R_2R_3R_4 \qquad (I)$$

wherein

R_1 represents H, a saturated or unsaturated, linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms, or a mixed hydrocarbon group thereof;
R_2 and R_3 each represent an alkyl group having from 1 to 3 carbon atoms, C^2, R_2 and R_3 together form a cycloalkyl group having from 3 to 6 carbon atoms, or when R_2 is H, R_3 represents an alkylthioalkyl group, an alkylsulfinylalkyl group, an alkylsulfonylalkyl group or an alkoxycarbonylmethyl group having from 2 to 7 carbon atoms;
R_4 represents a phenyl group, a benzyl group, a cyclohexyl group, a cyclohexylmethyl group, a phenyl group having a substituent selected from F, Cl, Br, I, a hydroxyl group, an alkoxy group having from 1 to 6 carbon atoms, a cyano group, a nitro group, an acetyl group, an amino group or an acetylamino group in the 2-, 3- or 4-position, a phenyl group having a methylenedioxy group, a trimethylene group or a tetramethylene group in the 2- and 3-positions or in the 3- and 4-positions, a 2-, 3- or 4-pyridyl group, a 2- or 3-furyl group, or a 2- or 3-thienyl group;
the configuration of aspartic acid containing a carbon atom in the C^1-position is (S), and the configuration containing a carbon atom in the C^2-position is (R), (S) or (RS), and
X represents a residue of a D-α-amino acid or a DL-α-amino acid such as D-alanine, D-α-aminobutyric acid, D-norvaline, D-valine, D-norleucine, D-leucine, D-isoleucine, D-alloisoleucine, D-t-leucine, D-serine, D-O-methylserine, D-threonine, D-O-methylthreonine, D-allothreonine, D-O-methylallothreonine, D-S-methylcysteine, D-methionine, D-phenylglycine or D- or DL-furylglycine, or a cyclic or acyclic α,α-dialkylamino acid residue having from 3 to 6 carbon atoms.

The hydrocarbon group represented by R_1 may be a saturated linear group which is a straight chain or a branched chain alkyl group, or an unsaturated straight chain or branched chain linear group, i.e. an alkenyl or alkynyl group, the group being unsubstituted or substituted with a saturated or unsaturated cyclic hydrocarbon group. The hydrocarbon group represented by R_1 may furthermore be a saturated or an unsaturated cyclic hydrocarbon group having one or more

unsaturated carbon atoms within the ring and/or within the substituent(s), the group being unsubstituted or substituted with one or more of the above linear hydrocarbons. As an example, the saturated cyclic group may be a cyclohexyl group and the unsaturated cyclic group may be an aromatic group such as a phenyl or benzyl group.

Mode of Carrying Out the Invention

The novel aspartyl dipeptide amide derivatives of the present invention are the compounds of formula (I) and salts thereof.

Examples of the salts of the compounds in the present invention include salts with alkali metals such as sodium and potassium; salts with alkaline-earth metals such as calcium and magnesium; salts with amines such as monoethanolamine; salts with inorganic acids such as hydrochloric acid and sulfuric acid; and salts with organic acids such as citric acid and acetic acid.

The aspartyl dipeptide amide derivatives of the present invention can be prepared by the usual peptide synthesis method (Basis of Peptide Synthesis and Experiments Thereof, by Izumiya et al., Maruzen, January 20, 1985). That is, a desired α-L-aspartyl-α-amino acid amide can be formed by first condensing an α-amino acid containing a protected amino group with the corresponding amine, then removing the protective group, condensing the resulting amino acid amide with L-aspartic acid in which a carboxylic acid in the β-position and an amino group are protected to form a dipeptide amide and then removing the protective groups, or by converting L-aspartic acid in which a carboxylic acid in the β-position and an amino group are protected to an active ester, reacting this ester with an α-amino acid, then reacting the reaction mixture with the corresponding amine to obtain a dipeptide amide, and thereafter removing the protective groups. Further, an N-alkyl-α-L-aspartyl-α-amino acid amide can be formed by reductively alkylating an α-L-aspartyl-α-amino acid amide with an aldehyde and a reducing agent [for example, NaB(OAc)3H] [Tetrahedron Letters, by A. F. Abdel-Magid et al., 31, 5595 (1990)], or reductively alkylating α-L-aspartyl-α-amino acid amide obtained by protecting a carboxylic acid in the β-position of aspartic acid with an aldehyde and a reducing agent and then removing the protective group. However, the method of forming the compounds of the present invention is not limited thereto. A β-alkylthioamine used in the compounds of the present invention can be formed by the method described in the literature [Tetrahedron Letters, by B. G. Donner, 36, 1223, (1995) or Tetrahedron Asymmetry, by G. A. Cran et al., 6, 1553 (1995)]. However, the method is not limited thereto. β-Phenyl-β-alanine used in the compounds of the present invention can be formed by a known method from benzaldehyde, ammonium acetate and malonic acid and be split into optically active substances by the method described in the literature [Chem. Ber., by E. Fischer et al., 43, 2020 (1910) or Tetrahedron, by H. H. Wasserman et al., 39, 2459 (1983)]. However, the method is not limited thereto.

As a result of the sensory evaluation, it was found that the compounds of the present invention and the salts thereof have a strong sweetness and their sweetness qualities are similar to that of sugar. For example, the degree of sweetness of α-L-aspartyl-D-α-aminobutyric acid (R)-α-methylthiomethylbenzylamide was approximately 4,000 times (that of sugar), the degree of sweetness of α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide was approximately 3,000 times (that of sugar), the degree of sweetness of α-L-aspartyl-D-isoleucine (R)-α-methylthiomethylbenzylamide was approximately 5,000 times (that of sugar), the degree of sweetness of N-3,3-dimethylbutyl-α-L-aspartyl-D-valine(R)-α-methylthiomethylbenzylamide was approximately 5,000 times (that of sugar), the degree of sweetness of α-L-aspartyl-D-valine (S)-α-methoxycarbonylmethylbenzylamide was approximately 1,500 times (that of sugar), and the degree of sweetness of α-L-aspartyl-D-valine-α-phenylcyclopentylamide was approximately 1,200 times (that of sugar). The half-lives (in a phosphate buffer of pH 3 at 70 C) of α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide, α-L-aspartyl-D-isoleucine (R)-α-methylthiomethylbenzylamide and α-L-aspartyl-D-valine (S)-α-methoxycarbonylmethylbenzylamide in an acidic aqueous solution were approximately 220 hours, 650 hours and 139 hours respectively, and these were by far stabler than that (approximately 23 hours under the same conditions) of aspartame.

The configurations of the aspartyl dipeptide derivatives formed and the results of the sensory evaluation thereof are shown in Table 1.

$$R_1\text{-}NHC^1H(CH_2COOH)CO\text{-}X\text{-}NH\text{-}C^2R_2R_3R_4 \quad (I)$$

Table 1

Structures[1] of aspartyl dipeptide amide derivatives and degrees of sweetness thereof						
X	R_1	$^1C^2$ -position	R_2	R_3	R_4	^{2}degrees of[2] sweetness
D-Ala	H	(R)	H	CH_2SCH_3	Ph	1000
D-Abu[3]	H	(R)	H	CH_2SCH_3	Ph	4000
D-Val	H	(R)	H	CH_2SCH_3	Ph	3000
D-Ile	H	(R)	H	CH_2SCH_3	Ph	5000
D-Val	3,3-Dimethylbutyl	(R)	H	CH_2SCH_3	Ph	5000
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	Ph	800
D-Val	H	(S)	H	$CH_2CO_2CH_3$	Ph	1500
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	4-CH_3O-Ph	200
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	2,3-CH_2O_2-Ph	250
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	4-HO-Ph	200
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	4-CH_3-Ph	200
D-Abu	H	(RS)	H	$CH_2CO_2CH_3$	c-C_6H_{11}	700
D-Val	H	(RS)	H	$CH_2CO_2CH_3$	c-C_6H_{11}	400
D-Abu	3,3-Dimethylbutyl	(RS)	H	$CH_2CO_2CH_3$	Ph	1250
D-Val	3,3-Dimethylbutyl	(RS)	H	$CH_2CO_2CH_3$	Ph	1250
D-Abu	3,3-Dimethylbutyl	(RS)	H	$CH_2CO_2CH_3$	c-C_6H_{11}	1250
D-Val	H	-	CH_3	CH_3	Ph	500
D-Ile	H	-	CH_3	CH_3	Ph	250
D-Abu	H	-	-$CH_2CH_2CH_2CH_2$-		Ph	750
D-Val	H	-	-$CH_2CH_2CH_2CH_2$-		Ph	1200

) Configurations of Asp containing C^1 are (S).
2) Relative to a degree of sweetness of a 4-% sucrose aqueous solution.
3) Abu =α-aminobutyric acid
1. C^2-configuration
2. Degree of sweetness

When the compounds of the present invention or the salts thereof are used as a sweetener, they may be used in combination with other sweeteners unless inviting any troubles.

Example 1

Synthesis of α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide

A solution (35 ml) of 4-N HCl / dioxane was added to 2.65 g (10.0 mmols) of N-tert-butoxycarbonyl-(R)-α-methylthiomethylbenzylamine, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was concentrated with the addition of 30 ml of ether to obtain (R)-α-methylthiomethylbenzylamine hydrochloride in a quantitative yield.

N-tert-butoxycarbonyl-D-valine (2.39 g, 11.0 mmols) and 10.0 mmols of the above-obtained (R)-α-methylthiomethylbenzylamine hydrochloride were dissolved in 60 ml of methylene chloride. Triethylamine (1.53 ml, 11.0 mmols), 2.11 g (11.0 mmols) of water-soluble carbodiimide hydrochloride and 1.49 g (11.0 mmols) of HOBt were added to the solution while being cooled to 0 C. The mixture was stirred for 1 hour while being cooled, and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 100 ml of water were added to the

residue, and the solution was extracted twice with 100 ml of ethyl acetate. The organic layer was washed twice with a 5-% citric acid aqueous solution, with 50 ml of a saturated aqueous solution of sodium chloride, twice with a 5-% sodium hydrogencarbonate aqueous solution and with 50 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain N-tert-butoxycarbonyl-D-valine (R)-α-methylthiomethylbenzylamide as a solid in a quantitative yield.

A solution (35 ml) of 4-N HCl / dioxane was added to 10.0 mmols of the above-obtained N-tert-butoxycarbonyl-D-valine (R)-α-methylthiomethylbenzylamide, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was further concentrated with the addition of 30 ml of ether. The residue was dissolved in 60 ml of methylene chloride, and 5.18 g (11.0 mmols) of N-tert-butoxycarbonyl-L-aspartic acid-β-tert-butyl ester dicyclohexylamine salt were then added thereto. Water-soluble carbodiimide hydrochloride (2.11 g, 11.0 mmols) and 1.49 g (11.0 mmols) of HOBt were added thereto while being cooled to 0 C. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 100 ml of water were added to the residue, and the solution was extracted twice with 100 ml of ethyl acetate. The organic layer was washed twice with a 5-% citric acid aqueous solution, with 50 ml of a saturated aqueous solution of sodium chloride, twice with a 5-% sodium hydrogencarbonate aqueous solution, and with 50 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and purified with PTLC to obtain 5.09 g (9.47 mmols) of N-tert-butoxycarbonyl-β-O-tert-butyl-α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide as a viscous oil.

A solution (45 ml) of 4-N HCl / dioxane was added to 5.09 g (9.47 mmols) of N-tert-butoxycarbonyl-β-O-tert-butyl--L-aspartyl-D-valine (R)- -methylthiomethylbenzylamide, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the mixture was stirred with the addition of 50 ml of ether. Subsequently, the supernatant was removed by decantation, and the residue was dried under reduced pressure. The residue was dissolved in 50 ml of water, and insoluble material was removed by filtration. To the filtrate were added 50 ml of methanol and 2 ml of 28-% ammonia water, and the solution was concentrated under reduced pressure. The residue was dissolved in a small amount of water and 200 ml of methanol, and 2 g of activated carbon were added thereto. The mixture was stirred at 50 C for a while. The activated carbon was removed by filtration, and the filtrate was concentrated to approximately one-fourth of its original volume. The crystals precipitated were collected by filtration, washed with a small amount of water, and dried under reduced pressure to give 2.80 g (7.34 mmols) of α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide as a solid.

^{1}HNMR (DMSO-d_6) δ:0.86 (d, 3H), 0.90 (d, 3H), 2.03 (s, 3H), 2.00-2.10 (m, 1H), 2.20 (dd, 1H), 2.42 (dd, 1H), 2.72-2.84 (m, 2H), 3.75 (dd, 1H), 4.27 (brt, 1H), 4.96 (q, 1H), 7.20-7.40 (m, 5H), 8.43 (brd, 1H), 8.59 (d, 1H).

ESI-MS 382.2 (MH^+)

Degree of sweetness (relative to sugar): 3,000 times

Example 2

Synthesis of α-L-aspartyl-D-alanine (R)-α-methylthiomethylbenzylamide

Example 1 was repeated except that N-tert-butoxycarbonyl-D-alanine was used instead of N-tert-butoxycarbonyl-D-valine to give α-L-aspartyl-D-alanine (R)-α-methylthiomethylbenzylamide as a solid in a total yield of 40.0%.

^{1}HNMR (DMSO-d_6) δ:1.30 (d, 3H), 2.06 (s, 3H), 2.29 (dd, 1H), 2.49 (dd, 1H), 2.74-2.88 (m, 2H), 3.69 (q, 1H), 4.32-4.41 (m, 1H), 4.94-5.02 (m, 1H), 7.25-7.41 (m, 5H), 8.50 (brd, 1H), 8.55 (d, 1H).
ESI-MS 354.3 (MH^+)
Degree of sweetness (relative to sugar): 1,000 times

Example 3

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (R)- - methylthiomethylbenzylamide

Example 1 was repeated except that N-tert-butoxycarbonyl-D-α-aminobutyric acid dicyclohexylamine salt was used instead of N-tert-butoxycarbonyl-D-valine to give α-L-aspartyl-D-α-aminobutyric acid (R)-α-methylthiomethylbenzylamide as a solid in a total yield of 53.4%.

^{1}HNMR (DMSO-d_6) δ:0.87 (t, 3H), 1.52-1.68 (m, 1H), 1.68-1.72 (m, 1H), 2.03 (s, 3H), 2.25 (dd, 1H), 2.44 (dd, 1H), 2.72-2.85 (m, 2H), 3.72 (dd, 1H), 4.27 (brq, 1H), 4.95 (q, 1H), 7.20-7.38 (m, 5H), 8.46 (brd, 1H), 8.58 (d, 1H).
ESI-MS 368.3 (MH^+)
Degree of sweetness (relative to sugar): 4,000 times

Example 4

Synthesis of α-L-aspartyl-D-isoleucine (R)-α-methylthiomethylbenzylamide

Example 1 was repeated except that N-tert-butoxycarbonyl-D-isoleucine was used instead of N-tert-butoxycarbonyl-D-valine to give α-L-aspartyl-D-isoleucine (R)-α-methylthiomethylbenzylamide as a solid in a total yield of 62.8%.

^{1}HNMR (DMSO-d_6) δ:0.84 (t, 3H), 0.90 (d, 3H), 1.04-1.17 (m, 1H), 1.39-1.49 (m, 1H), 1.78-1.87 (m, 1H), 2.04 (s, 3H), 2.20 (dd, 1H), 2.44 (dd, 1H), 2.80 (d, 2H), 3.75 (dd, 1H), 4.30 (brt, 1H), 4.97 (dd, 1H), 7.23-7.40 (m, 5H), 8.48 (brd, 1H), 8.64 (d, 1H).
ESI-MS 396.3 (MH^+)
Degree of sweetness (relative to sugar): 5,000 times

Example 5

Synthesis of α-L-aspartyl-D-valine (S)-α-methoxycarbonylmethylbenzylamide

N-tert-butoxycarbonyl-D-valine (5.34 g, 24.6 mmols) and 5.31 g (24.6 mmols) of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride (S:R = 2:1) were suspended in 100 ml of methylene chloride, and the suspension was maintained at 0 C. Triethylamine (3.78 ml, 27.1 mmols), 5.20 g (27.1 mmols) of water-soluble carbodiimide hydrochloride and 3.66 g (27.1 mmols) of HOBt were added thereto, and the mixture was stirred for 1 hour while being cooled and then overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and 150 ml of water were then added to the residue. The solution was extracted twice with 100 ml of ethyl acetate. The organic layer was washed twice with 100 ml of a 5-% citric acid aqueous solution, with 100 ml of a saturated aqueous solution of sodium chloride, twice with a 5-% sodium hydrogencarbonate aqueous solution and with 100 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and magnesium sulfate was then removed by filtration. The filtrate was concentrated under reduced pressure to obtain 9.27 g (24.5 mmols) of N-tert-butoxycarbonyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

A solution (60 ml) of 4-N HCl / dioxane were added to 9.27 g (24.5 mmols) of N-tert-butoxycarbonyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was further concentrated with the addition of 50 ml of ether. To the residue were added 100 ml of methylene chloride and 8.75 g (24.5 mmols) of N-benzyloxycarbonyl-L-aspartic acid-β-benzyl ester, and the mixture was maintained at 0 C. Triethylamine (3.75 ml, 26.9 mmols), 5.16 g (26.9 mmols) of water-soluble carbodiimide hydrochloride and 3.64 g (26.9 mmols) of HOBt were added thereto. The resulting solution was stirred for 1 hour while being cooled and then overnight at room temperature. One hundred milliliters of water were added to the reaction mixture, and the solution was extracted twice with 100 ml of ethyl acetate. The organic layer was washed twice with 100 ml of a 5-% citric acid aqueous solution, with 100 ml of a saturated aqueous solution of sodium chloride, twice with 100 ml of a 5-% sodium hydrogencarbonate aqueous solution and with 100 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and magnesium sulfate was then removed by filtration. The filtrate was concentrated under reduced pressure to obtain 13.6 g (22.0 mmols) of N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide (13.6 g, 22.0 mmols) was suspended in a mixed solvent of 150 ml of methanol and 5 ml of water, and 3.0 g of 5-% palladium on carbon having a water content of 50% were added thereto. The mixture was reduced at 50 C for 5 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was recrystallized from a mixture of methanol and water, and dried to give 3.18 g (8.08 mmols) of α-L-aspartyl-D-valine (S)-α-methoxycarbonylmethylbenzylamide.

^{1}HNMR (DMSO-d_6) δ:0.81 (d, 3H), 0.83 (d, 3H), 1.90-2.00 (m, 1H), 2.19 (dd, 1H), 2.40 (dd, 1H), 2.70-2.83 (m, 2H), 3.55 (s, 3H), 3.69-3.75 (m, 1H), 4.18 (brs, 1H), 7.20-7.35 (m, 5H), 8.39 (brs, 1H), 8.64 (d, 1H).
ESI-MS 394.3 (MH^+)
Degree of sweetness (relative to sugar): 1,500 times

Example 6

Synthesis of α-L-aspartyl-D-valine (RS)-α-cyclohexyl-β -methoxycarbonylethylamide

Example 5 was repeated except that (RS)-α-cyclohexyl-β -methoxycarbonylethylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-valine (RS)-α-cyclohexyl-β-methoxycarbonylethylamide as a solid in a total yield of 54.6%.

^{1}HNMR (DMSO-d_6) δ:0.79 (d, 3H), 0.82 (d, 3H), 0.80-1.75 (m, 13H), 1.85-2.03 (m, 1H), 2.20-2.58 (m, 4H), 3.54 (s, 3H), 3.73-3.80 (m, 1H), 3.97 (brs, 1H), 4.18 (brs, 1H), 7.85 (d, 0.5H), 7.89 (d, 0.5H), 8.32 (brs, 1H).

ESI-MS 400.3 (MH^+)

Degree of sweetness (relative to sugar): 400 times

Example 7

Synthesis of α-L-aspartyl-D-α-aminobutyric acid α-phenylcyclopentylamide

Example 5 was repeated except that N-tert-butoxycarbonyl-D-α-aminobutyric acid dicyclohexylamine salt was used instead of N-tert-butoxycarbonyl-D-valine and α-phenylcyclopentylamine instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride respectively to give α-L-aspartyl-D-α-aminobutyric acid α-phenylcyclopentylamide as a solid in a total yield of 54.9%.

^{1}HNMR (DMSO-d_6) δ:0.79 (t, 3H), 1.45-1.57 (m, 2H), 1.55-1.93 (m, 6H), 2.18-2.50 (m, 4H), 3.69 (m, 1H), 4.25 (brd, 1H), 7.10-7.35 (m, 5H), 8.12 (s, 1H), 8.30 (brd, 1H).
ESI-MS 362.3 (MH^+)
Degree of sweetness (relative to sugar): 750 times

Example 8

Synthesis of α-L-aspartyl-D-valine α-phenylcyclopentylamide

Example 5 was repeated except that α-phenylcyclopentylamine was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-valine α-phenylcyclopentylamide as a solid in a total yield of 61.9%.

^{1}HNMR (DMSO-d_6) δ:0.76 (d, 3H), 0.80 (d, 3H), 1.65-2.00 (m, 7H), 2.15-2.50 (m, 4H), 3.73 (m, 1H), 4.23 (brs, 1H), 7.10-7.35 (m, 5H), 8.14 (s, 1H), 8.25 (brd, 1H).
ESI-MS 376.3 (MH^+)
Degree of sweetness (relative to sugar): 1,200 times

Example 9

Synthesis of α-L-aspartyl-D-isoleucine α,α-dimethylbenzylamide

Example 5 was repeated except that N-tert-butoxycarbonyl-D-isoleucine was used instead of N-tert-butoxycarbonyl-D-valine and α,α-dimethylbenzylamine instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride respectively to give α-L-aspartyl-D-isoleucine α,α-dimethylbenzylamide as a solid in a total yield of 55.8%.

^{1}HNMR (DMSO-d_6) δ:0.82 (t, 3H), 0.83 (d, 3H), 0.96-1.11 (m, 1H), 1.29-1.41 (m, 1H), 1.53 (s, 3H), 1.56 (s, 3H), 1.69-1.80 (m, 1H), 2.29 (dd, 1H), 2.48 (dd, 1H), 3.79 (dd, 1H), 4.28 (brt, 1H), 7.13-7.33 (m, 5H), 8.24 (s, 1H), 8.32 (brd, 1H).
ESI-MS 364.3 (MH^+)
Degree of sweetness (relative to sugar): 250 times

Example 10

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α -methoxycarbonylmethylbenzylamide

(RS)-α-methoxycarbonylmethylbenzylamine hydrochloride (216 mg, 1.0 mmol) and 443 mg (1.0 mmol) of N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid were dissolved in 20 ml of methylene chloride. Water-soluble carbodiimide hydrochloride (211 mg, 1.1 mmols), 149 mg (1.1 mmols) of HOBt and 0.153 ml (1.1 mmols) of triethylamine were added thereto while being cooled to 0 C. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 50 ml of water were added to the residue, and the solution was extracted twice with 30 ml of ethyl acetate. The organic layer was washed twice with 25 ml of a 5-% citric acid aqueous solution, with 25 ml of a saturated aqueous solution of sodium chloride, twice with 25 ml of a 5-% sodium hydrogencarbonate aqueous solution and with 25 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to obtain 603 mg (0.997 mmols) of N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)- -methoxycarbonylmethylbenzylamide (603 mg, 0.997 mmols) was suspended in 30 ml of methanol and 2 ml of water, and 200 mg of 5-% palladium on carbon having a water content of 50% were added thereto. The solution was reduced under a hydrogen atmosphere at room temperature for 2 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The solid material precipitated was collected by filtration, and dried to give 289 mg (0.76 mmols) of α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide.

^{1}HNMR (DMSO-d_6) δ:0.73 (t, 1.5H), 0.82 (t, 1.5H), 1.40-1.70 (m, 2H), 2.15-2.30 (m, 1H), 2.39-2.50 (m, 1H), 2.70-2.85 (m, 2H), 3.54 (s, 3H), 4.19 (brs, 1H), 5.15-5.28 (m, 1H), 7.20-7.40 (m, 5H), 8.35 (brs, 1H), 8.58 (brd, 1H).
ESI-MS 380.3 (MH^+)
Degree of sweetness (relative to sugar): 800 times

Example 11

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α -methoxycarbonylmethyl-4-methoxybenzylamide

Example 10 was repeated except that (RS)-α-methoxycarbonylmethyl-4-methoxybenzylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-4-methoxybenzylamide as a solid in a total yield of 44.0%.

^{1}HNMR (DMSO-d_6) δ:0.72 (t, 1.5H), 0.81 (t, 1.5H), 1.40-1.65 (m, 2H), 2.22-2.34 (m, 1H), 2.45-2.53 (m, 1H), 2.68-2.82 (m, 2H), 3.54 (s, 3H), 3.72 (s, 3H), 3.69-3.77 (m, 1H), 4.16-4.20 (m, 1H), 5.10-5.20 (m, 1H), 6.86 (d, 1H), 6.87 (d, 1H), 7.21 (d, 1H), 7.24 (d, 1H), 8.39 (brd, 1H), 8.51 (d, 1H).
ESI-MS 410.3 (MH^+)
Degree of sweetness (relative to sugar): 200 times

Example 12

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-2,3-methylenedioxybenzylamide

Example 10 was repeated except that (RS)-α-methoxycarbonylmethyl-2,3-methylenedioxybenzylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-2,3-methylenedioxybenzylamide as a solid in a total yield of 53.4%.

^{1}HNMR (DMSO-d_6) δ:0.73 (t, 1.5H), 0.81 (t, 1.5H), 1.40-1.70 (m, 2H), 2.15-2.30 (m, 1H), 2.40-2.55 (m, 1H), 2.66-2.82 (m, 2H), 3.55 (s, 3H), 3.67 (brs, 1H), 4.18 (brs, 1H), 5.05-5.18 (m, 1H), 5.98 (s, 2H), 6.73-6.92 (m, 3H), 8.34 (brs, 1H), 8.47 (brd, 1H).
ESI-MS 424.3 (MH^+)
Degree of sweetness (relative to sugar): 250 times

Example 13

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-4-hydroxybenzylamide

Example 10 was repeated except that (RS)-α-methoxycarbonylmethyl-4-benzyloxybenzylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-4-hydroxybenzylamide as a solid in a total yield of 37.4%.

^{1}HNMR (DMSO-d_6) δ:0.72 (t, 1.5H), 0.81 (t, 1.5H), 1.40-1.70 (m, 2H), 2.24-2.38 (m, 1H), 2.45-2.56 (m, 1H), 2.65-2.82 (m, 2H), 3.53 (s, 3H), 3.70-3.80 (m, 1H), 4.19 (brs, 1H), 5.03-5.15 (m, 1H), 6.67 (d, 1H), 6.69 (d, 1H), 7.09 (d, 1H), 7.12 (d, 1H), 8.37 (brs, 1H), 8.45 (d, 0.5H), 8.48 (d, 0.5H).
ESI-MS 396.3 (MH^+)
Degree of sweetness (relative to sugar): 200 times

Example 14

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-4-methylbenzylamide

Example 10 was repeated except that (RS)-α-methoxycarbonylmethyl-4-methylbenzylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethyl-4-methylbenzylamide as a solid in a total yield of 61.4%.

^{1}HNMR (DMSO-d_6) δ:0.73 (t, 1.5H), 0.82 (t, 1.5H), 1.40-1.70 (m, 2H), 2.16-2.30 (m, 1H), 2.26 (s, 3H), 2.40-2.50 (m, 1H), 2.65-2.84 (m, 2H), 3.54 (s, 3H), 3.66-3.74 (m, 1H), 4.20 (brd, 1H), 5.10-5.23 (m, 1H), 7.08-7.24 (m, 4H), 8.37 (brs, 1H), 8.53 (brd, 1H).

ESI-MS 394.3 (MH^+)

Degree of sweetness (relative to sugar): 200 times

Example 15

Synthesis of α-L-aspartyl-D-α-aminobutyric acid (RS)-α-cyclohexyl-β-methoxycarbonylethylamide

Example 10 was repeated except that (RS)-α-cyclohexyl-β-methoxycarbonylethylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give α-L-aspartyl-D-α-aminobutyric acid (RS)-α-cyclohexyl-β-methoxycarbonylethylamide as a solid in a total yield of 87.2%.

^{1}HNMR (DMSO-d_6) δ:0.80 (t, 3H), 0.82-1.75 (m, 13H), 2.23-2.35 (m, 2H), 2.45-2.60 (m, 2H), 3.53 (s, 3H), 3.71-3.77 (m, 1H), 3.95 (brs, 1H), 4.19 (brs, 1H), 7.82 (d, 1H), 8.35 (brd, 1H).
ESI-MS 386.3 (MH^+)
Degree of sweetness (relative to sugar): 700 times

Example 16

Synthesis of α-L-aspartyl-D-valine α,α-dimethylbenzylamide

Example 10 was repeated except that N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-valine was used instead of N-benzyloxycarbonyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid and α,α-dimethylbenzylamine instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride respectively to give α-L-aspartyl-D-valine α,α-dimethylbenzylamide as a solid in a total yield of 27.6%.

^{1}HNMR (DMSO-d_6) δ:0.80 (d, 3H), 0.85 (d, 3H), 1.54 (s, 3H), 1.57 (s, 3H), 1.94-2.07 (m, 1H), 2.22 (dd, 1H), 2.44 (dd, 1H), 3.74 (dd, 1H), 4.25 (brs, 1H), 7.13-7.34 (m, 5H), 8.23 (s, 1H), 8.33 (brd, 1H).
ESI-MS 350.3 (MH^+)
Degree of sweetness (relative to sugar): 500 times

Example 17

Synthesis of N-3,3-dimethylbutyl-α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide

α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide (381 mg, 1.0 mmol) was suspended in 20 ml of THF, and 0.13 ml (1.0 mmol) of 3,3-dimethylbutyl aldehyde and 0.06 ml (1.0 mmol) of acetic acid were added thereto. The solution was maintained at 0 C, and 318 mg (1.5 mmols) of NaB (OAc)3H were added thereto. The mixture was stirred at 0 C for 1 hour and further overnight at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was neutralized with a 5-% sodium hydrogencarbonate aqueous solution. The reaction solution was concentrated, and then purified with silica-gel column chromatography (eluted with a mixture of ethyl acetate, chloroform and methanol at a ratio of 3:1:1.5) to give 180 mg (0.39 mmols) of N-3,3-dimethylbutyl-α-L-aspartyl-D-valine (R)-α-methylthiomethylbenzylamide as a solid.

^{1}HNMR (DMSO-d_6) δ:0.79 (s, 9H), 0.80-0.89 (m, 6H), 1.26-1.36 (m, 2H), 2.01 (s, 3H), 2.01-2.08 (m, 1H), 2.21 (dd, 1H), 2.35 (dd, 1H), 2.41-2.44 (m, 2H), 2.72-2.80 (m, 2H), 3.40 (dd, 1H), 4.23 (brt, 1H), 4.96 (q, 1H), 7.20-7.35 (m, 5H), 8.26 (d, 1H), 8.62 (d, 1H)
ESI-MS 466.4 (MH^+)
Degree of sweetness (relative to sugar): 5,000 times

Example 18

Synthesis of N-3,3-dimethylbutyl-α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide

N-tert-butoxycarbonyl-D-α-aminobutyric acid dicyclohexylamine salt (769 g, 2.0 mmols) and 431 mg (2.0 mmols) of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride were dissolved in 25 ml of methylene chloride. Water-soluble carbodiimide hydrochloride (383 mg, 2.2 mmols) and 297 mg (2.2 mmols) of HOBt were added thereto while being cooled to 0 C. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 50 ml of water were added to the residue, and the solution was extracted twice with 50 ml of ethyl acetate. The extract was washed twice with 25 ml of a 5-% citric acid aqueous solution, 25 ml of a saturated aqueous solution of sodium chloride, twice with 25 ml of a 5-% sodium hydrogencarbonate aqueous solution and with 25 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to obtain 730 mg (2.0 mmols) of N-tert-butoxycarbonyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

A solution (10 ml) of 4-N HCl / dioxane were added to 730 mg (2.0 mmols) of N-tert-butoxycarbonyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The residue was further concentrated with the addition of 30 ml of ether. The resulting residue was dissolved in 25 ml of methylene chloride and 0.31 ml (2.2 mmols) of triethylamine, and 647 mg (2.0 mmols) of N-tert-butoxycarbonyl-L-aspartic acid-β-benzyl ester were then added thereto. Water-soluble carbodiimide hydrochloride (383 mg, 2.2 mmols) and 297 mg (2.2 mmols) of HOBt were added thereto while being cooled. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 50 ml of water were added to the residue. The solution was extracted twice with 50 ml of ethyl acetate. The extract was washed twice with 25 ml of a 5-% citric acid aqueous solution, with 25 ml of a saturated aqueous solution of sodium chloride, twice with 25 ml of a 5-% sodium hydrogencarbonate aqueous solution and with 25 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to obtain 742 mg (2.0 mmols) of N-tert-butoxycarbonyl-β-O-benzyl-L-aspartyl-D- - aminobutyric acid (RS)- -methoxycarbonylmethylbenzylamide as a solid.

A solution (10 ml) of 4-N HCl / dioxane were added to 742 mg (2.0 mmols) of N-tert-butoxycarbonyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and 30 ml of a 5-% sodium hydrogencarbonate aqueous solution were added to the residue. The mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give 893 mg (1.90 mmols) of β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide as a viscous oil.

β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide (893 mg, 1.90 mmols) was dissolved in 15 ml of THF, and the solution was maintained at 0 C. To this solution were added 0.11 ml (1.90 mmols) of acetic acid, 0.24 ml (1.90 mmols) of 3,3-dimethylbutyl aldehyde and 605 mg (2.85 mmols) of NaB (OAc)3H. The mix-

ture was stirred at 0 C for 1 hour and further overnight at room temperature. To the reaction solution were added 30 ml of a saturated aqueous solution of sodium hydrogencarbonate, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified with PTLC to obtain 820 mg (1.48 mmols) of N-3,3-dimethylbutyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

N-3,3-dimethylbutyl-β-O-benzyl-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide (820 mg, 1.48 mmols) was dissolved in a mixed solvent of 35 ml of methanol and 2 ml of water, and 400 mg of 5-% palladium on carbon having a water content of 50% were added thereto. The mixture was reduced under a hydrogen atmosphere for 2 hours. Ten milliliters of water were added thereto, and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was dried under reduced pressure to give 604 mg (1.30 mmols) of N-3,3-dimethylbutyl-α-L-aspartyl-D-α-aminobutyric acid (RS)-α-methoxycarbonylmethylbenzylamide as a solid.

^{1}HNMR (DMSO-d_6) δ:0.70-0.85 (m, 3H), 0.79 (s, 4.5H), 0.87 (s, 4.5H), 1.30-1.70 (m, 4H), 2.55-2.85 (m, 6H), 3.54 (s, 1.5H), 3.56 (s, 1.5H), 3.81 (brs, 1H), 4.18-4.23 (m, 1H), 5.13-5.30 (m, 1H), 7.20-7.35 (m, 5H), 8.48 (d, 0.5H), 8.52 (d, 0.5H), 8.63 (d, 1H).
ESI-MS 464.4 (MH^+)
Degree of sweetness (relative to sugar): 1,250 times

Example 19

Synthesis of N-3,3-dimethylbutyl-α-L-aspartyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide

Example 18 was repeated except that N-tert-butoxycarbonyl-D-valine was used instead of N-tert-butoxycarbonyl-D-α-aminobutyric acid dicyclohexylamine salt to give N-3,3-dimethylbutyl-α-L-aspartyl-D-valine (RS)-α-methoxycarbonylmethylbenzylamide as a solid in a total yield of 75.7%.

^{1}HNMR (DMSO-d_6) δ:0.70-0.80 (m, 6H), 0.76 (s, 4.5H), 0.87 (s, 4.5H), 1.28-1.53 (m, 2H), 1.90-2.00 (m, 1H), 2.50-2.85 (m, 6H), 3.53 (s, 1.5H), 3.55 (s, 1.5H), 3.85-3.92 (m, 1H), 4.15-4.22 (m, 1H), 5.15-5.30 (m, 1H), 7.20-7.35 (m, 5H), 8.43 (d, 0.5H), 8.46 (d, 0.5H), 8.66 (brd, 1H).
ESI-MS 478.5 (MH^+)
Degree of sweetness (relative to sugar): 1,250 times

Example 20

Synthesis of N-3,3-dimethylbutyl-α-L-aspartyl-D-α-aminobutyric acid (RS)-α-cyclohexyl-β-methoxycarbonylethylamide

Example 18 was repeated except that (RS)-α-cyclohexyl-β-methoxycarbonylethylamine hydrochloride was used instead of (RS)-α-methoxycarbonylmethylbenzylamine hydrochloride to give N-3,3-dimethylbutyl-α-L-aspartyl-D-α-aminobutyric acid (RS)-α-cyclohexyl-β-methoxycarbonylethylamide as a solid in a total yield of 65.7%.

^{1}HNMR (DMSO-d_6) δ:0.75-0.85 (m, 3H), 0.87 (s, 9H), 0.90-1.75 (m, 13H), 2.25-2.42 (m, 1H), 2.50-2.80 (m, 5H), 3.54 (s, 3H), 3.80-4.00 (m, 2H), 4.10-4.23 (m, 1H), 7.89 (d, 1H), 8.47 (d, 0.5H), 8.54 (d, 0.5H).
ESI-MS 470.4 (MH^+)
Degree of sweetness (relative to sugar): 1,250 times

Claims

1. Novel aspartyl dipeptide derivatives represented by formula (I)

$$R_1\text{-NHC}^1\text{H}(CH_2COOH)CO\text{-X-NH-C}^2R_2R_3R_4 \quad (I)$$

wherein

R_1 represents H, a saturated or unsaturated, linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms, or a mixed hydrocarbon group thereof;
R_2 and R_3 each represent an alkyl group having from 1 to 3 carbon atoms, C^2, R_2 and R_3 together form a

cycloalkyl group having from 3 to 6 carbon atoms, or when R_2 is H, R_3 represents an alkylthioalkyl group, an alkylsulfinylalkyl group, an alkylsulfonylalkyl group or an alkoxycarbonylmethyl group having from 2 to 7 carbon atoms;

R_4 represents a phenyl group, a benzyl group, a cyclohexyl group, a cyclohexylmethyl group, a phenyl group having a substituent selected from F, Cl, Br, I, a hydroxyl group, an alkoxy group having from 1 to 6 carbon atoms, a cyano group, a nitro group, an acetyl group, an amino group or an acetylamino group in the 2-, 3- or 4-position, a phenyl group having a methylenedioxy group, a trimethylene group or a tetramethylene group in the 2- and 3-positions or in the 3- and 4-positions, a 2-, 3- or 4-pyridyl group, a 2- or 3-furyl group, or a 2- or 3-thienyl group;

the configuration of aspartic acid containing a carbon atom in the C^1-position is (S), and the configuration containing a carbon atom in the C^2-position is (R), (S) or (RS), and

X represents a residue of a D-α-amino acid or a DL-α-amino acid such as D-alanine, D-α-aminobutyric acid, D-norvaline, D-valine, D-norleucine, D-leucine, D-isoleucine, D-alloisoleucine, D-t-leucine, D-serine, D-O-methylserine, D-threonine, D-O-methylthreonine, D-allothreonine, D-O-methylallothreonine, D-S-methylcysteine, D-methionine, D-phenylglycine or D- or DL-furylglycine, or a cyclic or acyclic α,α-dialkylamino acid residue having from 3 to 6 carbon atoms,

and salts thereof.

2. The compounds of claim 1, wherein R_1 is H, X is a D-alanine residue, R_2 is H, R_3 is a methylthiomethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (R) or (RS).

3. The compounds of claim 1, wherein R_1 is H, X is a D-α-aminobutyric acid residue, R_2 is H, R_3 is a methylthiomethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (R) or (RS).

4. The compounds of claim 1, wherein R_1 is H, X is a D-valine residue, R_2 is H, R_3 is a methylthiomethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (R) or (RS).

5. The compounds of claim 1, wherein R_1 is H, X is a D-isoleucine residue, R_2 is H, R_3 is a methylthiomethyl group, R4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (R) or (RS).

6. The compounds of claim 1, wherein R_1 is a 3,3-dimethylbutyl group, X is a D-valine residue, R_2 is H, R_3 is a methylthiomethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (R) or (RS).

7. The compounds of claim 1, wherein R_1 is H, X is a D-α-aminobutyric acid residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

8. The compounds of claim 1, wherein R_1 is H, X is a D-valine residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

9. The compounds of claim 1, wherein R_1 is H, X is a D-α-aminobutyric acid residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a cyclohexyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

10. The compounds of claim 1, wherein R_1 is H, X is a D-valine residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a cyclohexyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

11. The compounds of claim 1, wherein R_1 is a 3,3-dimethylbutyl group, X is a D-α-aminobutyric acid residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

12. The compounds of claim 1, wherein R_1 is a 3,3-dimethylbutyl group, X is a D-valine residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a phenyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

13. The compounds of claim 1, wherein R_1 is a 3,3-dimethylbutyl group, X is a D-α-aminobutyric acid residue, R_2 is H, R_3 is a methoxycarbonylmethyl group, R_4 is a cyclohexyl group, the configuration containing the carbon atom in the C^1-position is (S), and the configuration containing the carbon atom in the C^2-position is (S) or (RS).

14. The compounds of claim 1, wherein R_1 is H, X is a D-valine residue, R_2 and R_3 are methyl groups, R_4 is a phenyl group, and the configuration containing the carbon atom in the C^1-position is (S).

15. The compounds of claim 1, wherein R_1 is H, X is a D-α-aminobutyric acid residue, C^2, R_2 and R_3 together form a cyclopentyl group, R_4 is a phenyl group, and the configuration containing the carbon atom in the C^1-position is (S).

16. The compounds of claim 1, wherein R_1 is H, X is a D-valine residue, C^2, R_2 and R_3 together form a cyclopentyl group, R_4 is a phenyl group, and the configuration containing the carbon atom in the C^1-position is (S).

17. A sweetener containing the novel aspartyl dipeptide amide derivatives of formula (I) or salts thereof as an active ingredient.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 11 1774

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	WO 94 00028 A (COCA-COLA) 6 January 1994 * the whole document *	1-17	C07K5/06
A	EP 0 691 346 A (AJINOMOTO) 10 January 1996 * the whole document *	1-17	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 October 1997	Masturzo, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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